Reply

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Response to Zevit

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We thank Dr. Noam Zevit for his interest in our paper on *"maintenance treatment of eosinophilic esophagitis (EoE) with swallowed topical steroids alters disease course over a 5-year follow-up period in adult patients"*. He elegantly underscores the current uncertainties in EoE long-term management.

First, the optimal target to treat has yet to be defined. Current guidelines lack explicit disease management endpoints given paucity of available data. We agree with Dr. Zevit that the concept of complete remission (=clinical, endoscopic and histological remission) has not been directly linked neither to prognosis nor disease progression. However, a combined and integrated assessment of patient-reported outcomes (PRO) and biological disease activity is reasonable since both PRO (symptoms) and biological markers (esophageal inflammation) are affected by EoE's natural history.[1] Furthermore, untreated EoE with ongoing inflammation has been shown to result in stricture formation in a time-dependent manner.[2] Endoscopy is currently needed to obtain biopsies anyway and a structured assessment of endoscopic disease activity adds an additional biological dimension. The validated EREFS score has been demonstrated to correlate well with histological improvement.[3] Until better, more effective and accessible outcome parameters are available, assessment of clinical, endoscopic and histological disease activity should be equally considered since these measures provide important complementary value. Activity in any of these dimensions is clinically meaningful.

Second, Dr. Zevit highlights the modest correlation between histology and clinical disease activity. This relationship has been previously described by Safroneeva et al, and remains a challenge in clinical practice.[4] It has yet to be defined whether ongoing symptoms despite histological remission are due to non-targeted disease aspects such as fibrostenotic complications, or dysmotility, or rather due to an ongoing inflammation that is not captured by pure appraisal of esophageal eosinophilia. Of note, higher doses and longer treatment with swallowed topical steroids appear to have a positive impact on symptoms regardless of esophageal eosinophilia.[5] This underscores the importance of ongoing inflammatory activity beyond eosinophilic infiltration. We strongly advocate against de-emphasizing symptoms as outcome measure in both clinical trials and daily practice for the following reasons: 1) despite above-mentioned modest correlation between histology and clinical activity, most symptomatic improvement can be captured by a cutpoint of <15 eos/hpf;[6] 2) regulatory authorities strongly encourage and require the use of PRO, 3) validated scores such as EEsAI PRO instrument are available; and 4) our ultimate goal in chronic management of EoE should be to treat the patient as a whole rather than just the esophagus. It is hard to tell a patient, that with a given medication his inflammation will resolve, but symptoms may persist to a degree that is not different compared to a placebo rate.

Third, it remains unknown whether or not there is a difference between chronic and episodic treatment of EoE. Current guidelines do not include recommendations in terms of long-term management strategies. While episodic treatment ("on" when symptoms, "off" when disease is controlled) might be

applicable to some patients, several findings indicate – however – a possible benefit from ongoing treatment: 1) cessation of treatment almost uniformly results in clinical and histological disease relapse within only few months;[7] 2) dose reduction is associated with loss of treatment response;[8] and 3) increasing frequency of use of steroids is associated with a lower risk for bolus impactions.[9] We agree that these data do not necessarily imply a worse long-term outcome with an on-off strategy, but with regards to the demonstrated safety and efficacy of swallowed topical steroids in the long-term, we advocate for ongoing chronic treatment strategies. Two possible therapeutic concepts applied at the Swiss EoE Clinic and at Mayo Clinic have been recently described and might help clinicians to deal with EoE in the long-term until more data are available.[10]

We appreciate the continued interest and insightful questions raised by Dr. Zevit. As he eagerly anticipates our findings over the next five years, so do we. We are looking forward to evolving long-term treatment data from different EoE centers around the world. With this, we will be able to include evidence-based recommendations regarding long-term EoE management in future EoE guidelines.

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CONFLICT OF INTEREST

Guarantor of the article: Thomas Greuter MD

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